

## Is Ovarian Tissue Cryopreservation and Transplantation Still Experimental? It Is a Matter of Female Age and Type of Cancer

**TO THE EDITOR:** We read with great interest the update of the American Society of Clinical Oncology (ASCO) guideline on fertility preservation in patients with cancer.<sup>1</sup> The authors spent much effort evaluating the current evidence on gonadotropin-releasing hormone agonists, because new evidence has accumulated since the first update of the ASCO guideline published in 2013. However, cryopreservation and transplantation of ovarian tissue were mentioned only briefly, even though this technique has also evolved considerably. The authors provided a general statement that this technique is still experimental; however, current evidence indicates that an overall classification of this technique should be replaced by a more sophisticated classification, which takes into consideration female age and type of cancer. For this reason, we would like to deepen the discussion regarding this point; in our opinion, it should be discussed much more intensively.

Defining a technique as experimental or established is indeed difficult, because clear criteria are required. Provoost et al,<sup>2</sup> representing the Special Interest Group Ethics in Law and the Special Interest Group Safety and Quality, both part of the European Society of Human Reproduction and Embryology, proposed a framework that distinguishes between experimental, innovative, and established therapies. They suggested applying the criteria of efficacy, safety, procedure, and effectiveness to assess new technologies and treatments. If all these criteria are fulfilled, a technique can be classified as established. These criteria can also be applied to classify ovarian tissue cryopreservation and transplantation in children, adults with malignant disease with a high risk of malignant cells in the ovaries (eg, those with leukemia), and adults with malignant disease with a low risk of malignant cells in the ovaries (eg, those with Hodgkin lymphoma or breast cancer).

Proof of principle (efficacy) is still lacking in children, because a live birth has only been achieved in one woman who had ovarian tissue frozen in the peripubertal stage,<sup>3</sup> but not in the prepubertal stage. Accordingly, the effectiveness (effectiveness) is also still unknown. Data on safety (safety) and technical performance (procedure) in children are also poor. Therefore, cryopreservation of ovarian tissue and transplantation must still be classified as experimental in children. This is in line with the recommendations of the expert meeting of the European Society for Blood Marrow Transplantation,<sup>4</sup> which also classified this technique as experimental.

In diseases such as leukemia, proof of principle (efficacy) has been demonstrated, because one child was born after transplantation of tissue frozen from a woman with leukemia.<sup>5</sup> In this case, the tissue transplantation was performed after small samples

were grafted into immunodeficient mice without developing signs of leukemia. However, safety data (safety) are still poor. The technique of cryopreservation is comparable between laboratories, but the technique of evaluating tissue before transplantation is not (procedure). Accordingly, data on the overall effectiveness (effectiveness) are also still poor, and therefore, cryopreservation and transplantation of ovarian tissue in adults with malignant disease and with a high risk of malignant cells in the ovaries, such as in leukemia, must still be classified as experimental. This is in line with Dolmans et al,<sup>6</sup> who described the risk of ovarian metastasis as high in leukemia, neuroblastoma, and Burkitt's lymphoma.

In diseases with a low risk of ovarian metastasis,<sup>6</sup> proof of principle (efficacy) has been demonstrated. Midterm safety data have been provided,<sup>7</sup> qualifying this technique as comparatively safe (safety). The procedure of cryopreservation by slow freezing, and evaluation of small tissue samples to exclude metastasis by histology is comparable between laboratories (procedure).<sup>8</sup> The effectiveness has been proven, with a cumulative live birth and ongoing pregnancy rate of 37.7% (effectiveness).<sup>7</sup> In the largest case series published so far, 16 deliveries were reported, six from women with previous Hodgkin lymphoma and six from women with previous breast cancer.<sup>9</sup>

In conclusion, we agree with the authors that this technique is still experimental in children and in adults with malignant disease with a high risk of malignant cells in the ovaries, such as in leukemia. However, in those with a low risk of ovarian metastasis, using the criteria of efficacy, safety, procedure, and effectiveness, as introduced by Provoost et al,<sup>2</sup> this technique should be classified as established and no longer experimental. This is also in line with the German, Austrian, and Swiss guidelines on fertility preservation.<sup>10</sup> We therefore strongly recommend categorizing this technique according to female age and previous malignant disease, because an inaccurate classification has not only clinical implications regarding counseling but also political implications regarding reimbursement.

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### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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